



BASIC CONSIDERATIONS

Renovascular hypertension (RVH) is defined as any vascular pathology that produces hypoperfusion of the kidney/s resulting, via various mechanisms, in the development of hypertension. Any occlusive aortic pathology distal to the aortic valve and extending to, and including, the renal arteries may result in RVH. These pathologies may produce severe hypertension and/or fluid overload.

In conventional practice ~ 95% of hypertensive patients will have primary or essential hypertension. Hypertension in this group is generally mild and is easily controlled on one or two anti-hypertensive medications.

In ~ 5% of hypertensive patients, they present with secondary or surgically correctible hypertension. Broadly speaking there are three groups of pathologies that produce severe secondary hypertension.

These are:

1. **Endocrine disorders**
 - Cushing's syndrome
 - Conn's syndrome
 - Pheochromocytoma
 - Hyperthyroidism
 - Hyperparathyroidism
 - Adreno-genital syndrome
2. **Renal parenchymal disorders**
 - Nephroblastoma (Wilm's tumor)
3. **Renovascular disorders**
 - Renal artery stenosis (RAS)
 - Coarctation of the aorta
 - The middle aortic syndrome

CLINICAL FEATURES THAT SUGGEST SECONDARY HYPERTENSION INCLUDE:

- Early onset of hypertension (< 30 years)
- Late onset of hypertension
- Severe hypertension (Blood pressure > 160/100)
- Malignant hypertension (Blood pressure > 180/120)
- Multi-drug requiring therapy for hypertension
- Medically refractory hypertension
- Epigastric bruits
- Grade 3 or 4 hypertensive retinopathy
- Flash pulmonary oedema (non-cardiogenic)
- Refractory angina in the elderly
- Clinical stigmata of endocrine disorders with severe hypertension

DIAGNOSTIC APPRAISAL

A diagnostic appraisal of a patient suspected of surgically correctible hypertension would incorporate the following where indicated:

An endocrine screen

- 9 am or midnight serum cortisol levels
- 24 hour urinary cortisol levels
- Serum aldosterone levels
- Plasma renin assays
- 24 hour urinary metanephrines / catecholamines
- Plasma catecholamines
- Thyroid function tests
- Parathyroid hormone levels
- Serum calcium and phosphate levels

Endocrine screen directed imaging

- Computed tomography (CT) of the abdomen, brain or chest
 - Abdomen (adrenal / extra-adrenal tumors)
 - Brain (pituitary tumors)

- Chest (Ectopic ACTH producing tumors, extra-adrenal pheochromocytoma, etc.)
- Ultrasound of the thyroid gland
- Radio-isotope scans
 - Iodo-cholesterol adrenal scans (primary hyperaldosteronism)
 - MIBG (meta-iodo-benzyl-guanidine) scan (pheochromocytoma)

Duplex Ultrasound of the kidneys

- Renal masses / tumors
- Discrepant renal lengths (this may suggest RAS)

MAG 3 Renogram with glomerular filtration rate (GFR)

This is a radioisotope scan that measure the percentage uptake in both kidneys as well as global renal excretion rate (GFR). One can use these measurements to calculate single-kidney GFRs.

Captopril renogram

Occasionally there may be some doubt relating to the functional significance of a moderate-severe RAS. Following a conventional renogram, a repeat scan is performed the following day after administering captopril. A positive test will show a decrease in uptake and excretion in the ipsilateral kidney suggesting a functionally significant RAS following captopril.

Vascular imaging (aortic and renal)

- Computed tomography angiography (CTA)
- Magnetic resonance angiography (MRA)
- Conventional digital subtraction angiography (DSA)

PATHOPHYSIOLOGY OF RVH

The pathophysiology of RVH relates to the activation of the renin-angiotensin-aldosterone-system (RAAS). The baroreceptors in the kidney are located in the juxta-glomerular

apparatus. These baroreceptors detect a drop in pressure and secrete renin. Renin converts angiotensinogen to angiotensin I, which is a weak vasoconstrictor. In the lungs, the angiotensin converting enzyme converts angiotensin I to angiotensin II. Angiotensin II produces hypertension via two mechanisms:

- It acts on angiotensin II (ATII) receptors resulting in vasoconstriction
- It promotes the production and release of aldosterone which results in fluid retention and volume expansion

The Goldblatt models, developed by ligating individual renal arteries in rats and documenting the clinical outcomes, may explain the basic clinical profiles. Three models were developed:

- Single renal artery stenosis / two kidney model
- Bilateral renal artery stenosis / two kidney model
- Renal artery stenosis in a solitary kidney model

In the single RAS / two kidney model, the patient develops hypertension but there is no volume expansion because the kidney with the normal renal artery produces a compensatory diuresis.

In the bilateral renal artery stenosis / two kidney model, and the RAS in a solitary kidney model, there is no normal kidney to effect a compensatory diuresis. As a result these patients present clinically with hypertension **and** volume overload.

Another aspect of the activated RAAS relates to the intra-renal site of action of ATII. Angiotensin II acts on ATII receptors located in the efferent arteriole as it leaves the glomerulus. By producing vasoconstriction of the efferent arteriole ATII preserves glomerular pressure and filtration in the setting of renal hypoperfusion. A patient taking an angiotensin

converting enzyme inhibitor (ACEI) will result in loss of this protective ATII effect on the efferent arteriole, resulting in decreased glomerular pressure and subsequent filtration. As a result the patient's creatinine levels will increase progressively. This ACEI-intolerance may represent a subtle clinical clue that RAS may be the cause of a patient's severe hypertension.

GOALS OF TREATMENT FOR RENOVASCULAR HYPERTENSION

The goals of treatment are the same irrespective of treatment modality.

- **To control blood pressure**
- **To preserve renal function**
- **To limit the treatment-related complications**

Blood pressure control may be:

- **A cure:** the patient's blood pressure is normal (<140/90) without any anti-hypertensive medication
- **An improvement:** the blood pressure is controlled with less anti-hypertensive medication (a reduction of 2 or more agents is considered significant).
- **Unchanged:** there is no improvement with treatment

RENAL ARTERY STENOSIS

Renal artery stenosis causes hypertension by activation of the RAAS. This results in a hyper-renin state and renin-dependent hypertension. Renal artery stenosis may be focal, diffuse or multiple.

Renal artery stenosis may be classified anatomically as:

- **Ostial RAS:** the stenosis involves the origin of the renal artery
- **Parostial RAS:** the stenosis commences < 10mm from the

origin but does not involve the origin of the renal artery

- **Truncal ("true") RAS:** the stenosis occurs > 10mm from the origin of the renal artery
- **Accessory RAS:** the stenosis occurs in an accessory (supernumerary) renal artery
- **Segmental RAS:** the stenosis occurs in a segmental branch of the renal artery
- **Mixed type RAS**
- **Renal artery occlusion**

Pathological classification of renal artery stenosis:

- **Atherosclerotic RAS** (90%)
- **Non-atherosclerotic RAS**
 - Fibromuscular dysplasia
 - Takayasu's disease
 - Renal artery dissection (generally associated with aortic dissection)
 - Developmental (neurofibromatosis)
 - Renal artery aneurysms (these may cause kinking of the renal artery)
 - Trauma
 - Juxta-renal saccular aortic aneurysms e.g. HIV associated aneurysms compressing the renal artery.
 - Radiation induced RAS
 - Anastomotic RAS involving transplant kidneys

Renal artery stenosis may be **mild** (low grade; < 30%), **moderate** (intermediate grade; 30% - 69%) or **severe** (high grade; 70% or more). Haemodynamically significant RAS has been estimated at > 60% stenosis.

Treatment modalities include:

- **Medical therapy**
- **Percutaneous transluminal renal angioplasty (PTRA - balloon angioplasty)**
- **Percutaneous transluminal renal angioplasty and stenting (PTRAS)**
- **Surgical revascularization**
- **Nephrectomy**

ATHEROSCLEROTIC RAS (ARAS)

Atherosclerotic disease can involve the renal arteries resulting in RAS manifesting clinically in two ways:

- **Severe hypertension.** Patients may present with newly diagnosed severe hypertension after the age of 50 or as previously well-controlled hypertension now requiring multiple anti-hypertensive agents with poor control.
- **Ischaemic nephropathy.** Patients present with rapidly progressive renal dysfunction generally < three months duration. This may or may not be related to recent administration of ACEIs. These patients may present with unexplained azotaemia.

Atherosclerotic RAS is found in 2 – 5% of hypertensive patients. It is an incidental finding in up to 40% of patients older than 75. It is found in ~ 15 – 25% of patients with end stage renal failure (ESRF). Studies suggest an association rather than a causal effect. Atherosclerotic RAS may be found in 30 – 40% of patients with peripheral arterial disease (PAD). Up to 15% of elderly patients undergoing a coronary angiogram may have a high grade RAS.

Atherosclerotic RAS is usually an ostial lesion. It represents an extension of an aortic plaque into the renal arteries.

Clinical features

Patients are the classic elderly group with risk factors for atherosclerosis. These include smoking, hypertension, diabetes mellitus, hyperlipidaemia and obesity. They may present with associated ischaemic heart disease (coronary artery disease), absent leg pulses (PAD – classically aorto-iliac disease) or carotid bruits (carotid disease). They may have an epigastric bruit on auscultation of the abdomen.

Treatment

Approximately 95% of patients will have mild to moderate RAS requiring only medical treatment. Medical treatment is similar to that of PAD and incorporates risk factor reduction, anti-platelet therapy, statins and anti-hypertensive treatment. Despite being counter-intuitive ACEIs are recommended in treatment regimens. Despite an initial increase in creatinine levels these agents have been shown to be reno-protective in the long term compared to the natural history of ARAS.

Only ~ 5% of patients with ARAS will have functionally significant high-grade stenosis to warrant further intervention.

Percutaneous Renal angioplasty and stenting (PTRAS)

This is a radiological interventional procedure where a balloon-expandable stent is deployed across a RAS. Given the co-morbidities these patients present with, PTRAS has evolved as first line treatment in this group where feasible.

Open surgical renal revascularization

Prior to PTRAS these procedures were the standard of care for ARAS. These procedures involve a laparotomy:

- Aorto-renal bypass procedure
- Renal endarterectomy (the plaque is surgically removed and the renal artery is patched)
- Extra-axial bypass procedures
 - Hepato-renal artery bypass
 - Spleno-renal artery bypass

Currently these procedures are reserved for patients fit for surgery and one of the following indications include:

- Patients requiring direct aortic reconstruction (e.g. abdominal aortic aneurysm repair)

- Patients with aorto-iliac occlusive disease (no access to perform PTRAS)
- Renal artery occlusion
- Sub-optimum PTRAS
- Complicated PTRAS
- Small caliber renal artery (RA) < 4mm
- Length of RAS > 2 cm
- RAS extending up to the renal bifurcation
- Truncal RAS with segmental RA involvement

Nephrectomy

This is a good option in patients with unilateral RAS with preserved renal function and severe hypertension. The requirements are:

- A small, shrunken, scarred kidney < 8cm in length
- Single kidney GFR < 10 ml/min /1.73 m²

Non-atherosclerotic RAS

These conditions may be uncommon but they share a few clinical features. These patients are generally young. Most will present with ages < 30. They do not have risk factors for atherosclerosis. They may present with symptomatic or complicated severe hypertension, renal dysfunction or both. An effort to exclude relevant endocrinopathies presenting with severe hypertension is essential here.

FIBRO-MUSCULAR DYSPLASIA (FMD)

Fibro-muscular dysplasia is a degenerative condition that involves branchless vessels and classically involves the renal, subclavian, carotid and iliac arteries. It is the pathology found in 10-20% of RAS. It affects young patients especially woman. Approximately one third will have involvement of segmental (branch) renal arteries as well. Approximately 35% of patients have bilateral disease. About 30% of patients will have progressive disease. However, unlike

ARAS, progression to renal artery occlusion and ESRF is rare.

Fibromuscular dysplasia may be classified pathologically as follows:

- **Medial type** (This is the most common type: 75 – 80%)
 - **Medial fibroplasia.** This classically produces areas of stenosis alternating with areas of dilatation resulting in a “string of beads” appearance on angiography (~ 65%). The “beads” are larger than the diameter of the renal artery.
 - **Perimedial fibroplasia** (<10%). Also presents with a “string of beads” appearance on imaging. The “beads” are the same diameter as the renal artery.
 - **Medial hyperplasia** (2%). Presents as a focal smooth stenosis.
- **Adventitial type**
 - **Adventitial fibroplasia**
- **Intimal type**
 - **Intimal fibroplasia.** Diffuse narrowing is a feature here (< 10%)

Diagnosis

Diagnosis is usually made on patient profile and DSA findings:

- The aorta is normal on angio-imaging
- The “string of beads” appearance is classical
- The disease profile usually affects the mid and distal thirds of the renal artery

Treatment

- The mainstay of treatment is **percutaneous transluminal balloon angioplasty**. Treatment results in a 50-60% cure rate and a 20 – 30% improvement rate. Recurrent stenosis are usually treated with repeat balloon angioplasty with good results.

- **Surgical revascularization** is reserved for:
 - Intimal type of FMD. These lesions tend to dissect easily and should not be offered here.
 - Complicated or sub-optimum balloon angioplasty
 - Associated significant renal branch vessel disease
- **Percutaneous transluminal angioplasty and stent (PTRAS).** This is an alternative to surgery, provided the distal renal artery is preserved for surgical bailout.
 - vessels (thoracic and /or abdominal)
 - RAS / renal artery occlusion
- Raised inflammatory markers (ESR and CRP)
- Histological features based on operative biopsy specimens:
 - Pan-arteritis (inflammatory response seen in all the layers of the arterial wall)
 - Giant-cell granulomas (non-caseating)

Treatment

- **Surgical revascularization.** This is the treatment of choice in these young patients.
 - Renal revascularization may be performed as an isolated procedure (see surgical treatment of ARAS for details)
 - Renal revascularization may be performed as part of a complex thoraco-abdominal aortic reconstructive procedure. This generally involves a thoracotomy and a laparotomy.
 - In our center **renal autotransplantation** has evolved as a suitable alternative to more expansive surgery with good results

TAKAYASU'S DISEASE

Takayasu's disease is a non-specific large vessel vasculitis that affects the aorta (resulting in an aortitis) and the aortic branch vessels.

- It predominantly affects young woman (~90%).
- A diagnostic feature is stenosis of the subclavian arteries, hence the reference "pulseless disease in a young woman".
- A common presentation in our center has been renovascular hypertension.
- It is not unusual to have bilateral RAS and/or renal artery occlusion
- RAS is generally the ostial or mixed type.

Diagnosis

- History of prodromal symptoms (fever, headaches, joint pains, muscle aches, carotidynia, etc.)
- Absent or diminished upper limb pulses associated with subclavian artery stenosis or occlusion.
- Patients may present with coronary artery disease, aortic or mitral regurgitation, or pulmonary hypertension.
- CTA findings:
 - Features of an aortitis (thick-walled aorta)
 - Occlusive disease of the aorta and aortic branch

- **Percutaneous transluminal renal balloon angioplasty.** This is not a durable procedure and recurrence rates are high. It may be considered as a bridge to surgery in patients needing to be optimized e.g. ventilator dependent patient with bilateral RAS and flash pulmonary oedema or cardiac failure.
- **PTRAS.** The considerations for balloon angioplasty also apply here. These are small caliber vessels that tolerate PTRAS poorly resulting in a high restenosis rate.

- **Medical therapy.** Patients with active disease are treated with immunosuppressive drugs.
 - Steroid therapy (**Prednisone**: a high induction dose is used; this is weaned down over time to a maintenance dose of 5 – 10 mg/day)
 - Methotrexate (15mg once weekly is generally prescribed)
 - Folic acid
 - Vitamin D supplements
 - Alternative immunosuppressive drugs may be considered. Modern management favours a steroid-sparing approach
- Aortic stenosis at or distal to the left subclavian artery
- Dilated proximal aorta and left subclavian artery
- Dilated tortuous intercostal arteries
- Post-stenotic dilatation of the aorta

4. Trans-oesophageal echocardiography (TOE)

Classification (anatomical types)

1. **Post-ductal**: commonest type; associated with bicuspid aortic valves in 40% of patients; patients generally survive till adulthood
2. **Pre-ductal**: generally associated with early death; may have multiple associated cardiac anomalies; few survive till adulthood
3. **Interrupted aorta**: most severe form; most are still-born

COARCTATION OF THE AORTA

This is a congenital narrowing of the thoracic aorta usually at the level of the ligamentum arteriosum. It is the commonest congenital cause of hypertension. The male to female ratio is 2:1.

Clinical features

Clinical presentation: **hypertension in a young patient** (generally lower limb hypertension). Patients may be:

- Asymptomatic (diagnosed incidentally)
- Symptomatic (headaches, syncope, claudication)
- Complicated (cardiac failure, stroke)
- Radio-radial delay or radio-femoral delay (delays in pulses palpated simultaneously)
- Bruit over the precordium

Diagnosis

1. ECG: shows features of left ventricular hypertrophy (LVH)
2. X-ray Chest
 - Cardiomegaly
 - Posterior inferior rib notching (due to dilated tortuous intercostal arteries)
3. CTA; MRA or conventional DSA

Medical treatment

Antihypertensive treatment

- B-Blockers
- Calcium channel blockers

Surgical treatment

- Patch aortoplasty
- Interposition bypass graft
- Resection and re-anastomosis

Interventional treatment

- Balloon angioplasty (usually performed in paediatric patients)
- Aortic stent (bare metal stent)
- Aortic stentgrafting (covered stent)

Clinical outcomes: Blood pressure is controlled in ~ 60% - 75% of cases.

THE MIDDLE AORTIC SYNDROME (MID-AORTIC SYNDROME)

The middle aortic syndrome is generally an acquired vascular

condition where various disease processes result in narrowing of the descending aorta (thoracic and/ or abdominal aorta) resulting in renin-dependent hypertension. The abdominal branches, including the renal arteries, may or may not be involved.

Pathologies associated with the middle aortic syndrome:

- **Takayasu's disease** (this is the dominant pathology)
- **Atherosclerosis**
- Congenital hypoplasia
- Von Recklinghausen's disease
- Fibromuscular dysplasia
- Tuberculous aortitis

Clinical features:

- Upper limb hypertension
- Radio-femoral delay
- Inter-scapular and/or abdominal bruits
- Patients may present with lower extremity claudication

Diagnosis:

- CTA
- Conventional DSA

Treatment:

1. Surgical

- Thoraco-abdominal aortic bypass, with or without visceral or renal revascularization

2. Endovascular

- Aortic stenting



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